REMARKS

Reconsideration of the application is respectfully requested. Claim 23 has been amended to correct a grammatical error. No new matter has been added. Claims 21, 23, 25, 27, 29, 31, 33, 35, and 37 are pending and at issue.

Indefiniteness Rejection

Claims 23, 29, and 35 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite. According to the Examiner, obtaining "a significant improvement ... as measured by the CGI improvement and severity subscale" is indefinite because the specification and claims do not indicate what change, or how much of a change, is considered a significant improvement.

The rejection is respectfully traversed, and reconsideration is requested.

CGI subscales (e.g., Clinical Global Impressions Improvement (CGI-I) and Clinical Global Impressions Severity (CGI-S)) are well known in the art, and significant improvements in patients can be determined using these subscales and standard statistical methods. For example, Burke et al., *J. Clin. Psychiatry*, 63(4):331-336 (April 2002) (copy attached as Exhibit A) is a study in which the CGI-I and CGI-S subscales were used to evaluate the efficacy and tolerability of escitalopram in the treatment of major depressive disorder (p. 332, right column, second full paragraph; and p. 333, Tables I and 2). According to Burke, the decrease from baseline in the CGI-S and the effect on the CGI-I for escitalopram (at doses of both 10 mg/day and 20 mg/day) "were statistically significantly superior to those observed for placebo treatment" (p. 333, Efficacy). Thus, Burke demonstrated a significant improvement in patients as measured by the

claimed CGI subscales. Two other articles, each predating the priority date of this application, discuss use of the CGI-S subscale to assess treatment of depression with paroxetine, fluoxetine, or buproprion. *See* Chouinard, et al., *J. Affective Disorders*, 54:39-48 (1999); and Reimherr, et al., *Clin. Therapeutics*, 20(3)505-516 (1998) (copies attached as Exhibits B and C, respectively). Like Burke, Chouinard and Reimherr further demonstrate that CGI subscales were known in the art and used to identify significant patient improvement. *See* Chouinard at p. 45, Table 6; and Reimherr at p. 511, Figure 2.

In view of the foregoing, the claims are definite and Applicants respectfully request that this rejection be withdrawn.

Obviousness Rejection

Claims 21, 23, 25, 27, 29, 31, 33, 35, and 37 have been rejected under 35 U.S.C. § 103(a) as obvious over Patris et al. (*Int. Clin. Psychopharm.* 11:129-136 (1996)) in view of Boegesoe et al. (U.S. Patent No. 4,943,590), and Bilski et al. (U.S. Patent No. 4,764,361). The Examiner cites Patris as disclosing the use of citalopram for the treatment of patients with major depression, and also teaches the assessment of treatment efficacy by measuring the MADRS score and the CGI severity and improvement scales. The Examiner cites Boegesoe as disclosing that almost the entire 5-HT uptake inhibition activity of citalopram resides in escitalopram. The Examiner states that Bilski discloses the oxalate and crystalline oxalate salts of an S-enantiomer of a compound, but does not disclose escitalopram. According to the Examiner, the use of the oxalate or crystalline oxalate salt of escitalopram for the treatment of severe depression would have been obvious in view of the teachings in these references.

The rejection is respectfully traversed, and reconsideration is requested.

The present inventors have discovered that escitalopram is surprisingly effective for the treatment of severe depression in patients having a MADRS score of at least 29. The specification describes a placebo-controlled clinical study involving 468 subjects. The mean MADRS total score of the subjects was approximately 29 (p. 6, line 21, to p. 7, line 9). A description of the protocol and results for this study can also be found in Lepola et al., *Int. Clin. Psychopharm.*, 18(4):211-7 (2003) (copy attached as Exhibit D). In the study, subjects were treated with 20 mg/day citalopram, 10 mg/day escitalopram, or placebo for the first four weeks of the study, with the option of doubling the dosages at week 4 or week 6 (Lepola at p. 213). After eight weeks of treatment, the adjusted mean change in MADRS total score for escitalopram was 2.9 points better than placebo (the mean change in MADRS total score was 15.0 points for the escitalopram group, compared to only 12.1 points for the placebo group) (Lepola at p. 213, left column, and Fig 1). This was a statistically significant result ($p=0.002$). Citalopram, on the other hand, did not yield a statistically significant improvement (Lepola at p. 213, left column and Fig 1).

The data from this study also demonstrate the statistically significant ($p<0.05$) therapeutic superiority of escitalopram over placebo after one week of treatment, as measured by the CGI-S subscale (Lepola at p. 215, Fig. 3). In contrast, the change in CGI-S score for the citalopram group was not statistically significant compared to placebo (Lepola at p. 215, Fig. 3).

Furthermore, the superior efficacy of escitalopram would not have been expected by one of ordinary skill in the art in view of the cited references. Citalopram is a racemate, containing both R-citalopram and escitalopram. Boegesoe teaches that almost the entire 5-HT

uptake inhibition activity of citalopram resides in the S-enantiomer (col. 2, lines 40-42). Based on Boegesoe, escitalopram would be expected, at best, to be twice as potent as citalopram (*see* specification, p. 2, lines 13-15). Escitalopram, however, was found to be more than twice as potent in the study. In the first four weeks of the study, one group received 20 mg citalopram (which contains about 10 mg escitalopram) and another group received 10 mg escitalopram. A person of ordinary skill in the art would have expected similar therapeutic efficacy to be observed in both treatment groups during this four week period because each group received approximately 10 mg of escitalopram. In contrast, the experimental results revealed that treatment with escitalopram was therapeutically superior to citalopram ($p<0.01$) (*see* Fig. 1 of Lepola).

A person of ordinary skill in the art would not have expected that administration of escitalopram alone would provide a therapeutic efficacy that is so superior to that achieved when both enantiomers were administered together (i.e., superior to the administration of citalopram). The inventors surprisingly discovered that the R-enantiomer in citalopram has a *negative* effect on escitalopram resulting in citalopram's inferior efficacy in severely depressed patients (*see* specification, p. 2, lines 13-14). None of the cited references teach or suggest the detrimental influence of the R-enantiomer, or that administration of escitalopram alone would provide the demonstrated superior therapeutic effect over racemic citalopram.

Finally, while Bilski describes oxalate and crystalline oxalate salts of the (S) isoform of a racemic mixture, it does not specifically disclose or suggest whether escitalopram would form an oxalate salt or whether such a salt would be crystalline.

In view of the foregoing, claims 21, 23, 25, 27, 29, 31, 33, 35, and 37 are not obvious over Boegesoe, Patris, and Bilski. Therefore, Applicants respectfully request that the rejection be withdrawn.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____
Jay P. Lessler
Registration No.: 41,151
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant